An invitation to Participate in a Community Resource

Col. Harland D. Sanders Award
American College of Medical Genetics
March 27, 2009

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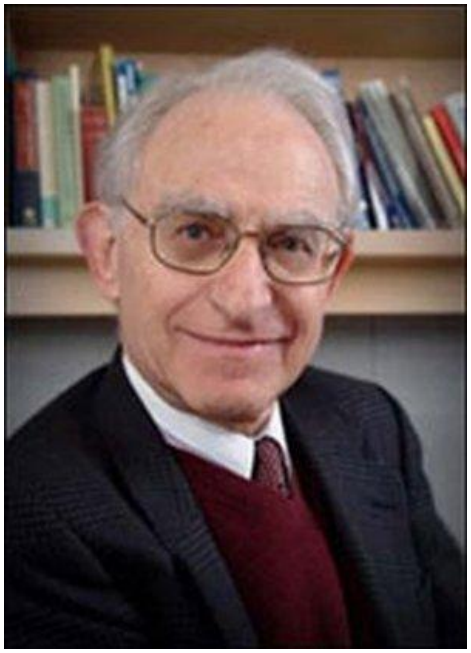
Principal Investigator, GeneTests
Professor, Pediatrics
University of Washington, Seattle

- Past
- Present
- Future

Mentors

Judith Hall



Arno Motulsky

Sponsors


Seattle Children's
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NCBI


NATIONAL INSTITUTES OF HEALTH
National Institutes of Health
The Nation's Medical Research Agency


UNIVERSITY of WASHINGTON

www.genetests.org

Information resource for healthcare providers to help integrate genetic testing into patient care

Located at
University of Washington
Seattle, WA

Funded by
National Institutes of Health

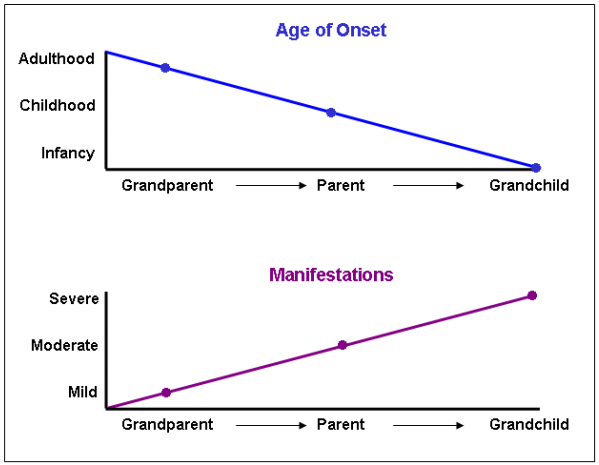
- ***GeneReviews*:** "User manual" for genetic testing for specific diseases
  - >475 *GeneReviews*
  - One new Review added each week
- **Laboratory Directory:** "Yellow Pages" of genetics labs
  - ~ 610 Clinical and research laboratories
  - ~1700 Inherited diseases
- **Clinic D** ·290 res
- **Illustrat** :ounse

anticipation: The tendency in certain genetic disorders for individuals in successive generations to present at an earlier age and/or with more severe manifestations; often observed in disorders resulting from the expression of a **trinucleotide repeat mutation** that tends to increase in size and have a more significant effect when passed from one generation to the next

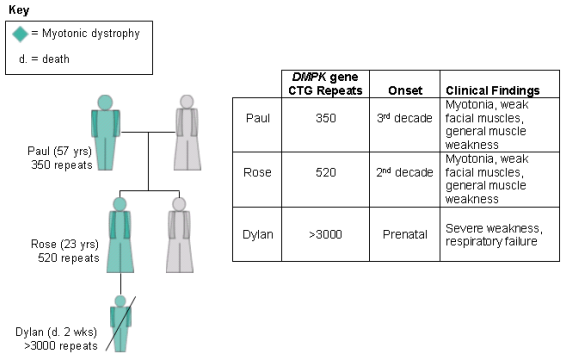
Case Example (anticipation): Myotonic dystrophy

Paul is a 57-year-old man with myotonic dystrophy, a neuromuscular disorder caused by a trinucleotide repeat mutation inherited in an autosomal dominant manner. Paul noticed muscle weakness in his late 20s and now has difficulty opening jars and climbing stairs. His 23-year-old daughter, Rose, experienced onset of muscle cramping and weakness as a teenager. Her son, Dylan, born after a pregnancy complicated by polyhydramnios and poor fetal movement, was extremely hypotonic and expired at two weeks of age of respiratory failure. Trinucleotide repeat analysis of the *DMPK* gene reveals that Paul has 350 CTG repeats, Rose has 520 repeats and Dylan over 3000 repeats, consistent with the observed increase in severity of the disorder in subsequent generations.

Learn More



Case Example



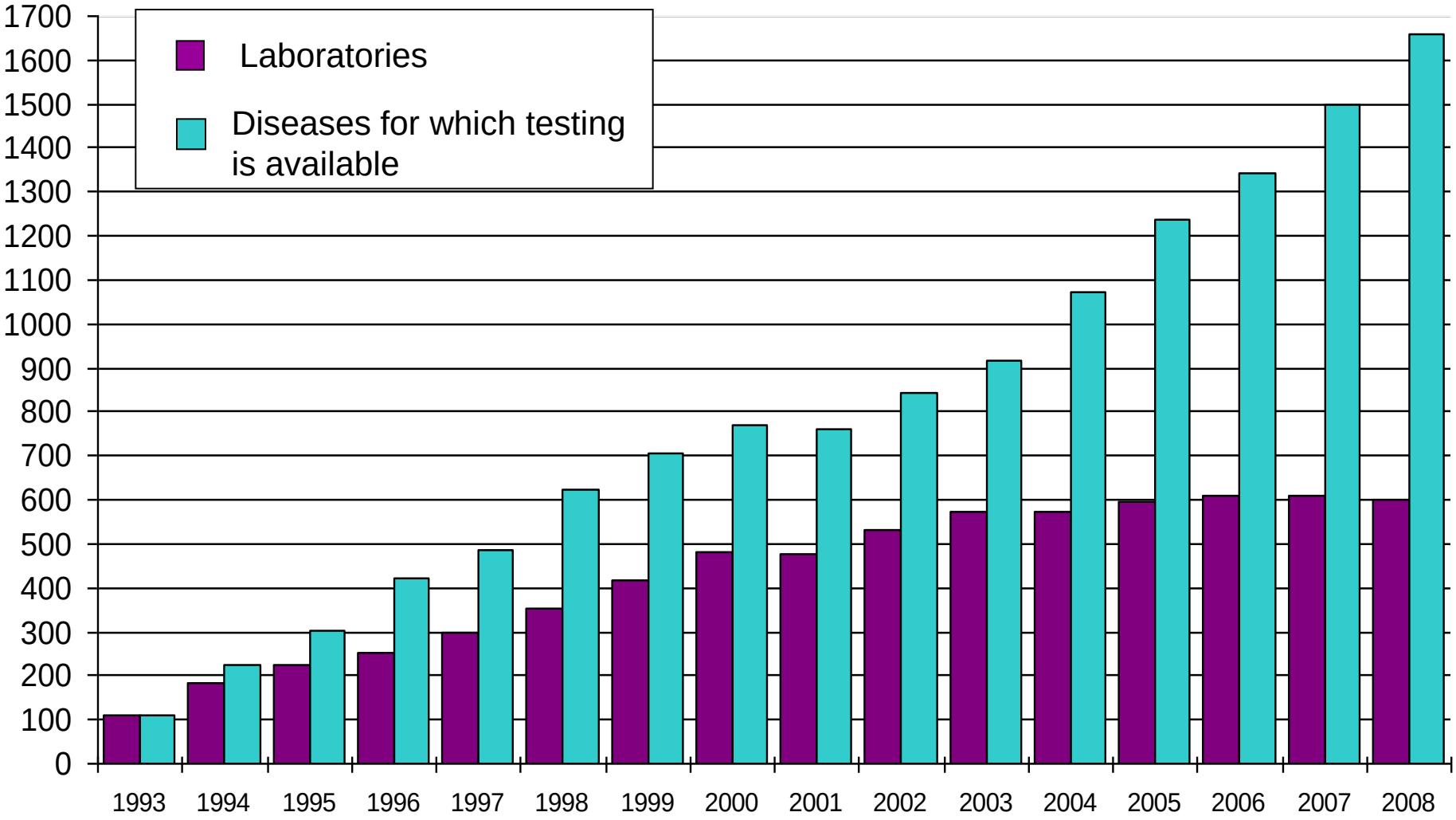
	DMPK gene CTG Repeats	Onset	Clinical Findings
Paul	350	3rd decade	Myotonia, weak facial muscles, general muscle weakness
Rose	520	2nd decade	Myotonia, weak facial muscles, general muscle weakness
Dylan	>3000	Prenatal	Severe weakness, respiratory failure

Focus

Molecular genetic testing for inherited disorders

- **Test menu ever-changing**
  - New genes
  - New test methods
- **Many labs, each testing for a few diseases**
- **Molecular genetic test uses**
  - Medical care
  - Personal decision-making

GeneTests: Growth of Laboratory Directory



Data source: GeneTests database (2008) / www.genetests.org

- Past
- Present
- Future

Information Conduit

- Scientists
- Colleagues
- Patients

GENETests

Standard Terminology

Gene symbol: HGNC

Mutation naming: HGVS nomenclature with reference sequence and version

Disease Naming

- Gene-based lumping and splitting of phenotypes
- What disease is this?

Vocabulary: What are we saying?

Sporadic vs Simplex:
Recurrence risk implications

- Sporadic = Chance event
- Simplex = Single occurrence in a family
  - Autosomal recessive
  - X-linked
  - Autosomal dominant: *de novo* mutation, reduced penetrance
  - Alternate paternity/adoption

- Past
- Present
- Future

GENETests

Common Complex Diseases

- What is the best way for GeneReviews/ Laboratory Directory to provide clinically useful information on complex diseases?
- Goal: Help medical geneticists & (more importantly) primary care providers

Ratings of Evidence

- For what?
  - ?Clinical utility/personal utility
  - ?Test sensitivity, specificity
- Who develops the rating scale?
- Who applies it?

GENETests

Community Resource

Contact us:

Errors

Innovative Ideas

Refer:

Labs/clinics

New users

Volunteer: Write a *GeneReview*

GENETests

Community Resource

- Specialty editors?
- Expanding the concept of “peer-review”?

Thank you for this honor

GENETests Staff

Principal Investigator Roberta A Pagon, MD

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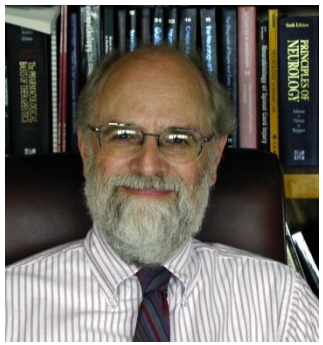

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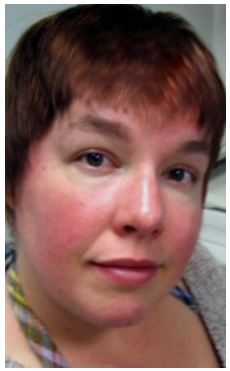

Sarah Pharris
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Thank you